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The overall aim of this research is to investigate the neural circuit mechanisms of attentional and discriminative processing of somatosensory stimuli which are cues for limb movement. These issues are being addressed mainly through use of multi-single neuron recording techniques, which we have recently developed. In the past granting period this approach has been used to record from ensembles of single neurons through microwire electrode arrays chronically implanted in the forepaw/forelimb areas of the somatosensory (SI) and motor (MI) cortices in awake behaving rats. These animals are trained to place their forepaw on a bar and move it up or down immediately upon detecting a vibratory stimulus imposed on the bar. Initially, only neurons in the SI responded to the sensory cue. After the rat learned to perform to criterion in the task, however, neurons in the MI cortex also responded at relatively short latency to the sensory cue. This suggests that transmission through a trans-cortical sensorimotor loop can be enhanced through training. Additional progress has been made on several other projects which provide necessary background information for this investigation.

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ANNUAL TECHNICAL REPORT

AFOSR-90-0266

"CORTICAL MECHANISMS OF ATTENTION, DISCRIMINATION, AND MOTOR RESPONSE TO SOMAESTHETIC STIMULI"

4-1/90 to 3-31-91

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I. SUMMARY

The overall aim of this research is to investigate the neural circuit mechanisms of attentional and discriminative processing of somatosensory stimuli which are cues for limb movement. These issues are being addressed mainly through use of multi-single neuron recording techniques, which we have recently developed. In the past granting period this approach has been used to record from ensembles of single neurons through microwire electrode arrays chronically implanted in the forepaw/forelimb areas of the somatosensory (SI) and motor (MI) cortices in awake behaving rats. These animals are trained to place their forepaw on a bar and move it up or down immediately upon detecting a vibratory stimulus imposed on the bar. Initially, only neurons in the SI responded to the sensory cue. After the rat learned to perform to criterion in the task, however, neurons in the MI cortex also responded at relatively short latency to the sensory cue. This suggests that transmission through a trans-cortical sensorimotor loop can be enhanced through training. Additional progress has been made on several other projects which provide necessary background information for this investigation.

II. RESEARCH OBJECTIVES

Objective A. Develop technology for simultaneous many neuron recording.

Status: Major progress has been made in the several areas of development of techniques for multi-single neuron recording. First, through Spectrum Scientific in Dallas, TX, we have developed apparatus capable of recording and discriminating up to 64 single neurons simultaneously from one animal. These are recorded through arrays of 25 or 50μM stainless steel microwire electrodes chronically and permanently implanted during an initial surgery. We have consistently found that if one waits 2-3 weeks after surgical implantation, excellent single unit recordings can be routinely obtained through chronically implanted microwire electrodes. The basis for this recording quality is unknown, but since isolation improves with time after surgery, it is possible that a gliotic encapsulation of neurons near the wire tips may be involved. These recordings are extremely stable (e.g. by comparison with 5-10MΩ etched tungsten electrodes), allowing single neurons to be recorded over many hours, days, or longer. A multichannel digital signal processor is used for digital spike waveform discrimination, and also for archival storage of the digitized waveforms.

Brain interface: Currently, each microwire array is premanufactured in "hats" containing two rows of 8 microwires apiece, spaced at exact 200-500μ intervals. These arrays can be implanted across cortical subzones, e.g. to cover the forepaw representations of the MI and SI cortices. Similarly, such arrays can cross the whisker representations of the thalamic VPM and POm nuclei. Other hats contain two bundles of 8 microwires apiece. These can be implanted in deeper structures such as trigeminal or dorsal column nuclei. Since three of these hats can easily be fit on a rat's head, 48 microwires can be stereotaxically implanted in appropriate target nuclei. As an example, in one recent surgery 48 microwires were implanted in one rat, distributed among the following sites along the afferent path from the whiskers: trigeminal ganglion, chief sensory trigeminal nucleus, VPM and POm thalamus, SI barrelfield cortex, and zona incerta. Discriminable units are typically obtained from 30-70% of the implanted microwires, but since many microwires record 3-4 discriminable units it should be possible to record 64 neurons with 48 microwires.

Recording apparatus and computers: Recently obtained electronic apparatus (custom made by Spectrum Scientific; see Methods:Recording apparatus) allow up to 64 units to be recorded simultaneously. Purchase of one additional 32 channel digital signal processor board will allow 64 spikes to be simultaneously discriminated. Finally, the PI's data acquisition and analysis software, previously implemented on (relatively slow) Data General S-20 computers, have now been translated for use on our two Motorola VME-147 systems, which increases our spike data acquisition, storage and analysis capacity to at least 100 channels.

Surgical implantation: The accuracy of electrode placement during surgery is assured by stereotaxic placement of microwires, and also by recording neural activity through the microwires during the implantation. Since nearly all of the target nuclei contain well delimited somatotopic maps of the body, the locations of receptive fields recorded through these electrodes during implantation, and also during

experimentation, is definitive of their placement within the nuclei. Further verification of electrode placement can be obtained subsequently through use of a dental X-ray which shows the locations of the metallic microwires relative to skull landmarks in frontal, horizontal, and sagittal views. Finally, histological reconstruction is carried out after all recording experiments are finished. The Prussian Blue reaction is used to mark specific electrode sites.

Objective B. **Record neuronal ensembles at multiple processing levels in the sensorimotor cortex in awake rats performing sensory cue directed forelimb movements.** Status: The following experimental paradigms have been carried out:

1. **(described in Pub. 17 in Publication list below:) Multineuronal responses in the SI and MI cortex during learning of a stimulus cued motor task.** Rats were trained to hold down a bar and release it upon receiving a vibratory cue. During this behavior, ensembles of single neurons were recorded simultaneously from cutaneous (GZ) and proprioceptive (PGZ) areas of the SI cortical forepaw representation, and also in the MI cortical forelimb area. Each neuron was first identified as to its receptive field and motor correlate before recording it over the cued motor task. Neurons with cutaneous receptive fields were able to follow a 50 Hz vibrational stimulus, but not a 100 Hz stimulus. Neurons with proprioceptive receptive fields exhibited smaller responses to the cue, but also discharged in relation to the motor response. Initially, neurons in the MI cortex did not respond to the vibratory cue, but responded strongly to it after learning to perform to criterion in the task. Similarly, serial connections (as measured by spike- triggered cross-correlations) from the SI cortex to the MI cortex began to appear after the rat learned the task. These findings suggest that subtle plastic rearrangements may occur in the connections within and between the SI and MI cortices over the time course of behavioral training paradigms which utilize these circuits.

2. **Sensory modulation at different levels of the somatosensory system.**

Pub. 3: Modulation of afferent transmission to single neurons in the ventroposterior thalamus during movement in rats. This paper describes studies on sensory gating in the VPL thalamic forepaw area of rats. While previous experiments in the SI cortex[18,19,20] had demonstrated an overall 71% suppression of paw stimulus induced input from the paw during treadmill locomotion, in the thalamus only a 30% reduction was found.

Pub. 6: Movement-induced modulation of afferent transmission to single neurons in the ventroposterior thalamus and somatosensory cortex in rat. This paper reports on differences in movement related suppression of short vs. longer latency responses to the paw stimulation (explained in Exp. Design:1a). Our available evidence suggests the short latency responses arise exclusively through the dorsal column nuclei, whereas the longer latency responses may be transmitted in part through extralemniscal systems. It was found that at the cortical level, both the short and long latency responses were strongly suppressed during movement, while at the thalamic level, only the long latency responses were strongly suppressed.

3. **Use of spike-triggered cross-correlations to measure serial connections between simultaneously recorded neurons in awake, behaving rats.**

Pub. 11: Heterosynaptic and behavioral modulation of functional connections between neurons simultaneously recorded in cortex and thalamus. Spike-triggered cross-correlations between pairs of simultaneously recorded neurons can be used to characterize and measure serial (putatively monosynaptic) transmission between those neurons. Such "serial" connections are distinguished from the more nonspecific "common input" correlations by the their extremely discrete, short latency (1-4 msec), and short duration (1-3 msec) responses in post-spike histograms. Several types of serial connections have been recorded so far, including local cortico-cortical, thalamocortical, corticothalamic, and cuneothalamic. See Exp. Design:1d for full details.

Pub. 19: Movement dependent modulation of functional connections between simultaneously recorded neurons at multiple levels of the lemniscal system in rat. This paper describes dynamic modulatory effects of limb movement on the efficacy of serial connections between neurons simultaneously recorded in the SI cortex and its afferent pathways. In general, movement was found to suppress

transmission through serial connections to neurons in the SI cortex from the VPL thalamus and from other neurons in the SI cortex. In contrast, serial connections from the cuneate nucleus to the VPL thalamus were observed to be facilitated during movement, and during specific phases of limb movement. These demonstrations of movement related modulation of efficacy of connections between single neurons tended to parallel our previous findings that sensory responses to stimulation of the paw are gated during movement.

Objective C. **Carry out background neuroanatomical and neurophysiological experiments appropriate to this work.** Status: Several studies were carried out, resulting in the following publications:

1. Neuroanatomical and neurophysiological studies of paths for somatosensory information flow to, and within the SI cortex of rat.

Pub. 1: The somatosensory cortex of rat. In R. Tees and B. Kolb Eds. The Neocortex of Rat. This chapter presents an extensive survey of the current state of our knowledge of the neuroanatomy and electrophysiology of the rat somatosensory cortex. Particular emphasis is placed on the subject of this grant, ie. behavioral control of sensory transmission through the neurons in this area. This is supported by previously published and also new unpublished research data from this laboratory.

Pub. 9: Ontogeny of corticocortical projections of the rat somatosensory cortex. This paper reports results of fluorescent retrograde tracer injections in the SI cortex of developing and adult rats. These findings extend our previous findings[27], identifying three distinct sources of local cortico-cortical connections in the rat SI. These include projections emanating from layers III, V, and VIb. The ipsilateral projections come from distinct layers of cells in layer Va and Vb, with callosal projection neurons interdigitated between.

Pub. 5: A major direct GABAergic pathway from zona incerta to neocortex. and Pub. 14: Functional characteristics of a direct GABAergic pathway from zona incerta to neocortex in rodents and primates. Pub. 5 reported neuroanatomical studies which demonstrated that the pathway from the zona incerta (ZI) to the neocortex, previously thought to be small, is quite large in the rat, is GABAergic, and projects somewhat topographically to different cortical areas, especially the SI cortex. In Pub. 14, receptive field mapping experiments showed that ZI neurons respond robustly to low threshold cutaneous stimulation, forming a rough body map in the ZI. Recordings of ZI neurons in awake rats also responded to somatosensory stimuli, especially during alerting or orienting behavior.

2. Basis for motor cortex involvement in sensory modulation

In an effort to define the effects of motor cortex stimulation on lemniscal system relay nuclei, single units were recorded in the dorsal column nuclei, VP thalamus, and SI cortex in anesthetized rats. In each of these regions three types of experiments were carried out: 1) the nuclei were mapped to define their receptive fields and their pattern of representation of the cutaneous periphery. 2) The pattern of motor cortical influence on these regions was assessed by microstimulating the MI cortex at half of the current threshold to evoke limb movements. 3) these cortical stimuli were used as conditioning stimuli to assess modulation of neuronal responses to test sinusoidal flutter vibration stimulation of the cutaneous receptive fields on the forepaw.

Pub. 2: Mapping the effects of motor cortex stimulation on somatosensory relay neurons in the rat thalamus: Direct responses and afferent modulation. The MI stimulation had a small but measurable modulatory effect on sensory transmission through the VPL thalamus. The strongest modulation was expressed on neurons peripheral in the VPL. Overall, these findings support the idea that the MI's strongest modulatory effects on the lemniscal pathway are at the SI cortical level.

Pub. 7: Mapping the effect of SI cortex stimulation on somatosensory relay neurons in the rat thalamus: direct responses and afferent modulation. Stimulation of the SI cortex produced facilitory followed by inhibitory effects on VPL neurons, both in direct responses and in transmission of afferent transmission through these nuclei. The initial excitatory effects were quite spatially circumscribed, whereas the subsequent inhibitory effects were more broadly felt. These findings are consistent with a model including direct, topographically specific, and excitatory effects of SI corticothalamic efferents on

neurons in the VPL and in the thalamic reticular nucleus (nRT). The nRT neurons could provide most of the subsequent inhibitory responses. Thus, the SI cortex could shape and control its sensory input from the VPL through these corticothalamic systems.

III. PUBLICATIONS

Published papers

1. Chapin, J.K. and Lin, C.-S. (1990) The somatosensory cortex of rat. In R. Tees and B. Kolb Eds. The Neocortex of Rat Academic Press.
2. Shin, H.-C. and Chapin, J.K. (1990) Mapping the effects of motor cortex stimulation on somatosensory relay neurons in the rat thalamus: direct responses and afferent modulation. Brain Res. Bull. 24:257-265.
3. Shin, H-.C. and Chapin, J.K. (1990) Modulation of afferent transmission to single neurons in the ventroposterior thalamus during movement in rats. Neurosci. Letters 108:116-120.
4. Patel, I.M. and Chapin, J.K. (1990) Ketamine effects on somatosensory cortical single neurons in behaving rats. Anesth. & Analg. 70:635-644.
5. Lin, C.-S., Nicolelis, M.A.L., Schneider, J.S. and Chapin, J.K. (1990) A major direct GABAergic pathway from zona incerta to neocortex. Science 248:1553-1556.
6. Shin, H.-C. and Chapin, J.K. (1990) Movement-induced modulation of afferent transmission to single neurons in the ventroposterior thalamus and somatosensory cortex in rat. Exp. Brain Res. 81:515-522.
7. Shin, H.-C. and Chapin, J.K. (1990) Mapping the effect of SI cortex stimulation on somatosensory relay neurons in the rat thalamus: direct responses and afferent modulation. Somatosens. & Motor Res. 7:421-434.
8. West, M.O., Carelli, R.M., Pomerantz, M., Cohen, S.M., Gardner, J.P., Chapin, J.K., and Woodward, D.O. (1990) Single units in the dorsolateral striatum of the rat are correlated with specific locomotor limb movements. J. Neurophys. 64:1233-1246.

9. Nicolelis, M.A.L., Lin, C.-S., and Chapin, J.K. (1991) Ontogeny of corticocortical projections of the rat somatosensory cortex. Somatosens. & Motor Res. 8:193-200.
10. Nicolelis, M.A.L., Chapin, J.K. and Lin, C.-S. (1991) Thalamic plasticity induced by early whisker removal in rats. Brain Res. 561:344-349.

Abstracts:

11. Chapin, J.K. and Shin, H.-C. (1990) Heterosynaptic and behavioral modulation of functional connections between neurons simultaneously recorded in cortex and thalamus. Abst. in Soc. Neurosci. Mtg. 1990
12. Utz, J.P., Nicolelis, M.A. and Chapin, J.K. (1990) Emergent properties revealed in multi-layer neuronal network models: feedforward vs. feedback inhibition. Abst. in Soc. Neurosci. Mtg. 1990
13. Fisher, T.M., Nicolelis, M.A.L. and Chapin, J.K. (1990) Chaotic dimensionality of cortical neuronal discharge patterns is altered by anesthetic state. Abst. in Soc. Neurosci. Mtg. 1990
14. Lin, C.-S., Nicolelis, M.A.L., Chapin, J.K. and Kaas, J.H. (1990) Functional characteristics of a direct GABAergic pathway from zona incerta to neocortex in rodents and primates. Abst. in Soc. Neurosci. Mtg. 1990
15. Nicolelis, M.A.L., Lin, C.-S. and Chapin, J.K. (1990) Neonatal whisker removal preserves a normally transient projection from the medial geniculate to the somatosensory cortex in rats. Abst. in Soc. Anat. Mtg. 1990
16. Kosobud, A.E, Shin, H.-C. and Chapin, J.K. (1990) Effect of ethanol on neurons in somatosensory (SI) cortex and VPL thalamus in awake, behaving rats. Abst. in Soc. Neurosci. Mtg. 1990
17. Chapin, J.K. and Mariano, R.T. (1991) Multineuronal responses in the SI and MI cortex during learning of a stimulus cued motor task. Abst. in Soc. Neurosci. 248.17

Papers Submitted or in Preparation:

18. Chapin, J.K. and Nicolelis, M.A.L. Use of multivariate statistics to characterize population coding within simultaneously recorded neurons in behaving animals. (Submitted)
19. Chapin, J.K. and Shin, H.-C. Movement dependent modulation of functional connections between simultaneously recorded neurons at multiple levels of the lemniscal system in rat. (In Preparation)

IV. PARTICIPATING PROFESSIONALS:

A. John K. Chapin, Ph.D., P.I.
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B. Miguel A. L. Nicolelis, M.D., Ph.D. Research Associate
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V. INTERACTIONS

A. Oral Presentations (by the P.I.):

1. Symposium on CNS Effects of Norepinephrine at the Winter Conference on Brain Research (Vail, Colorado, January, 1991).

2. Sessions on Cerebral cortex and Somatosensory system at the Meeting of the Society for Neuroscience (St. Louis, October, 1990, see Abstracts in the Publication list).

3. Invited seminar at the Dept. of Anatomy, Pennsylvania State University Med. Cntr. at Hershey, PA

4. Invited seminar at the Dept. of Anatomy and Neuroscience, U. of Tennessee

B. Interactions with other AFOSR funded laboratories:

Collaborated closely on development of many-neuron recording technology with:

Donald J. Woodward, Ph.D.
Dept. Cell Biology and Neuroscience
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Dallas, TX

Samuel A. Deadwyler, Ph.D.
Dept. of Physiology
Bowman Gray Sch. Med.
Wake Forest Univ.
Winston-Salem, NC

C. Consulting:

Served as an ad hoc reviewer of grants submitted to AFOSR.

VI. Discoveries, Inventions or patent disclosures:

None beyond those discussed above. No patent disclosures.